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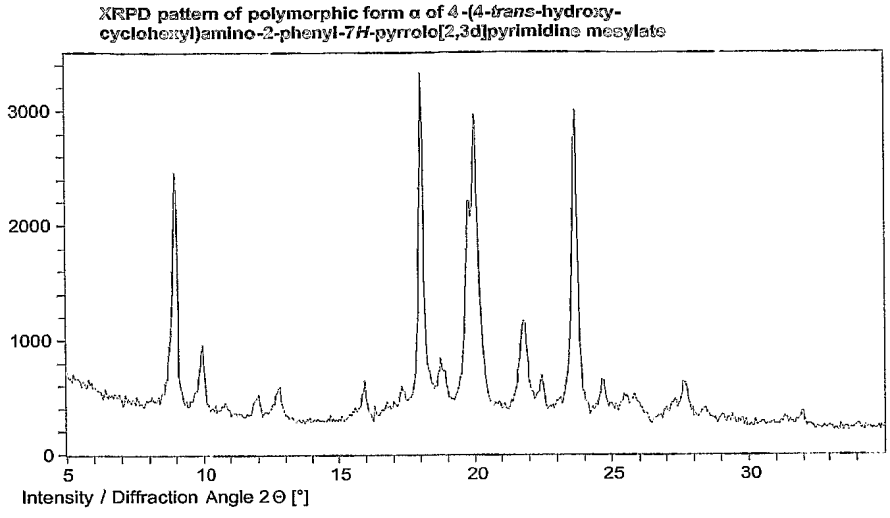
(54) Title: 4-(4-TRANS-HYDROXYCYCLOHEXYL)AMINO-2-PHENYL-7H-PYRROLO‘2, 3D! PYRIMIDINE HYDROGEN MESYLATE AND ITS POLYMORPHIC FORMS



(57) Abstract: The present invention relates to the novel compound 4- (4-trans-hydroxycyclohexyl)amino-2-phenyl-7H--pyrrolo[2,3d]pyrimidine hydrogen mesylate, the polymorphic α and β forms thereof and a method for the production of said compounds.

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4-(4-TRANS-HYDROXYCLOHEXYL)AMINO-2-PHENYL-7H-PYRROLO'2,3D!PYRIMIDINE MESYLATE AND ITS POLYMORPHIC FORMS

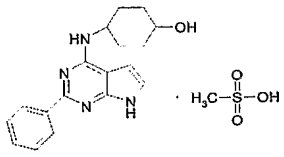
The present invention relates to the novel compound 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate, different polymorphic forms thereof and a method for the production of said compounds.

4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine is disclosed in WO 99/62518 (compound 18 on page 53) and is a selective Adenosine-1 Receptor agonist that may be used in the treatment of essential hypertension, congestive heart failure and renal failure.

During further development of said compound in the mentioned indications, it appeared that the compound as disclosed in WO 99/62518 has the se rious drawback of a low solubility in gastrointestinal fluids.

It is the object of the present invention to provide a salt of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine that is a crystalline, homogeneous and stable product and that has superior solubility properties.

This object can be achieved, according to the present invention by the hydrogen mesylate salt of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]-pyrimidine. In the framework of the present applicati on this compound is further referred to as 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]-pyrimidine mesylate. The compound has the following structure:



In contrast to the camphorsulfonate, mono -ethanedisulfonate, mono-isethionate, phosphate and sulfate salts the mesylate salt is highly soluble in water. Further 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]-pyrimidine mesylate appears to be very stable at ambient conditions.

Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidi-ne mesylate was found to exist in two polymorphic forms, further indicated as polymorphic forms α and β. Both polymorphic forms have improved solubility, although form α has a better solubility than form β . Form α is metastable with respect to form β. Form β is the currently known stable form.

Substantially pure form α can be obtained in a laboratory setting by adding a solution of methane sulfonic acid in methanol to a suspension of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine in methanol, followed by the addition of isopropanol. Substantially pure form β can be obtained by adding a solution of methane sulfonic acid in ethanol to a solution of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine in ethanol, followed by the addition of water and stirring. The pure form β can also be obtained by stirring samples of pure form α in a mixture of ethanol and water.
The term substantially pure means a purity of at least 90%, preferably at least 95%, even more preferred 97% and most preferred at least 99%.

The polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate according to the present invention is defined by the following physicochemical characteristics:

(i) An X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2 θ) at: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7. Diffraction angles are indicated as mean values (± 0.1 °) of six independent measurements. The complete XRPD pattern for the polymorphic form α shown in Figure 1.

(ii) An infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3246, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743. The complete IR spectrum for the polymorphic form α is shown in Figure 2.

(iii) A melting point at approximately 248 °C (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form α is shown in Figure 3.

The polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate according to the present invention is defined by the following physicochemical characteristics:

(i) An X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2 θ) at: 9.3, 11.6, 12.2, 17.6, 18.0, 18.6, 19.3, 20.8, 23.4, 26.5. Diffraction angles are indicated as mean values (± 0.1 °) of four independent measurements. The complete XRPD pattern for for the polymorphic form β is shown in Figure 4.

(ii) An infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732. The complete IR spectrum for the polymorphic form β is shown in Figure 5.

(iii) A melting point at approximately 220 °C (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form β is shown in Figure 6.

4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine is known to be useful in treating and/or preventing essential hypertension, congestive heart failure and renal failure in mammals. 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine can also be administered as its hydrogen mesylate. It is effective over a wide dosage range. The term "therapeutically effective amount" in the framework of the present invention refers to an amount capable of diminishing the adverse symptoms of a particular disease in a subject. With a "subject" is meant a human subject of either sex and of any age, but also any non-human animal, particularly a domestic or companion animal (such as a cat, dog, monkey, cow or horse). Preferred dosage is in the range of from about 0.01 to about 200 mg body weigth per day. In the treatment of adult humans range of about 0.1 to about 100 mg in single or divided doses is particularly preferred. The particular dose of compound administered according to the present invention will, however, be determined by the particular circumstances surrounding the case, including the weight, the age, the severity of the symptoms and the individual response of the patient and will also depend on the route of administration. Therefore the above mentioned dosage range are not intended to limit the scope of the present invention in any way.

4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate may be administered in different ways, e.g orally, transdermally and/or parenterally. In the case of acute heart failure the compound is preferrrably administered parenterally. Compositions intended for oral, transdermal and/or parenteral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. Such compositions may comprise one or more materials selected from the group consisting of coloring agents, flavoring agents,

sweetening agents and preservatives. Formulations for oral use may be tablets which may contain the active ingredient in admixture with pharmaceutically acceptable excipients, such as binding agents (e.g. starch, acacia, gelatin), lubricating agents (e.g. stearic acid, magnesium stearate, talc), granulating and disintegrating agents (e.g. corn starch, alginic acid) and inert diluents (e.g. calcium phosphate, sodium phosphate, calcium carbonate, sodium carbonate, lactose). Formulations for oral use may also be soft gelatin capsules wherein the active ingredient is mixed with water or an oily medium such as liquid paraffin, peanut oil, or olive oil or hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent such as kaolin, calcium carbonate or calcium phosphate.

The following examples are only intended to further illustrate the invention, in more detail, and therefore these examples are not deemed to restrict the scope of the invention in any way.

Example 1. Preparation of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate.

701 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine prepared according to the method described in WO 99/62518 are suspended in 4.5 L methanol. a solution of 240 g methane sulfonic acid in 750 mL methanol is added under stirring, leading to a clear solution. The mixture is concentrated to 1900 g, then 5.5 L isopropanol are added at room temperature and the mixture is stirred for 44 h. The product is filtrated, washed four times with 0.5 L isopropanol, each and dried for 40 h at 95 °C in a vacuum drying oven to give 780 g of the title compound as crystalline modification α.

Example 2. Preparation of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate.

2.00 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine (= 6.50 mmol) was dissolved in 70 ml of acetone at reflux temperature. Under stirring at reflux temperature there was added a solution of 0.62 g of methanesulfonic acid (= 6.50 mmol) in 7 ml of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. After this the reaction mixture was cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 1 hour at 2 °C. The product was collected by filtration, washed twice with 5 ml of acetone and dried

under vacuo at 50 °C for 24 hours. This gave 2.49 g of crystalline modification α (= 95 % c/c).

The polymorphic form α was also obtained from the solvents acetonitrile and 2-butanone, according to a similar procedure.

Example 3. Preparation of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate.

2.00 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine (= 6.50 mmol) was dissolved in a mixture of 45 ml of acetone and 5 ml of water at reflux temperature. Under stirring at reflux temperature there was added a so lution of 0.62 g of methanesulfonic acid (= 6.50 mmol) in 5 ml of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. After this the reaction mixture was cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 45 hours at room temperature. The product was collected by filtration, washed twice with 5 ml of acetone and dried under vacuo at 50 °C for 24 hours. This gave 2.26 g of crystalline modification β (= 86 %).

The polymorphic form β was also obtained from the solvent mixtures acetonitrile/water and 2-butanone/water, according to a similar procedure.

Example 4. Rearrangement of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate into its polymorphic form β.

5302 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate modification α was stirred in 20 l of ethanol and 2 L of water for 5 days at ambient temperature. The product was filtrated and dried at 70 °C for 40 h in a circulating air drier to give 3444 g of the title compound as crystalline modification β.

Example 5. Analytical methods.

XRPD patterns were measured on a diffractometer using monochromatic CuKα radiation (tube voltage 40 kV, tube current 40 mA).IR spectra were recorded on a Fourier transform IR spectrometer in attenuated total reflectance (silicon crystal) with a spectral resolution of 2 cm^{-1} using a deuterated triglycine sulfate detector.

Melting points were determined on a DSC apparatus as onset temperatures of the melting endotherm using 40 µL aluminum crucibles with a pierced lid. Temperature program: heating from 25 °C up to 300 °C with 10 K min^{-1}. N_2 atmosphere at a flow of 60 mL min^{-1}.

Solubility measurements were carried out with the shake flask method according to the OECD guideline at 25°C (OECD Guideline for testing of chemicals, No. 105 (issued 12 May 1981)).

Example 6. Solubility of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine and its mesylates polymorphic form α and β.

Measurement of the solubility of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine and its mesylates polymorphic form α and β in purified water gave the following results

Compound	Solubility in mg/l
Base	0.0059
Polymorph α	77
Polymorph β	18.5

Claims

1. 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate.

2. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α) exhibiting an X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2 θ) at: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7.

3. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by an X-ray powder diffraction (=XRPD) pattern shown in Figure 1..

4. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), exhibiting an infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3246, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743.

5. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by a complete IR spectrum shown in in Figure 2.

6. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), exhibiting an melting point at approximately 248 °C.

7. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by a complete DSC trace shown in in Figure 3.

8. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), exhibiting an X-ray powder diffraction (=XRPD) pattern having characteristic

reflexes (expressed in degrees of diffraction angle 2 θ) at: 9.3, 11.6, 12.2, 17.6, 18.0, 18.6, 19.3, 20.8, 23.4, 26.5.

9. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), characterized by an X-ray powder diffraction (=XRPD) pattern shown in in Figure 4.

10. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), exhibiting an infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732.

11. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), characterized by a complete IR spectrum shown in in Figure 5.

12. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), exhibiting an melting point at approximately 220 °C.

13. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), characterized by a complete DSC trace shown in in Figure 6.

14. A pharmaceutical composition comprising an effective amount of the compound according to claims 1-13.

15. A pharmaceutical composition according to claim 14, intended for parenteral use.

16. A compound as claimed in any of the claims 1 - 13 for use in medicine

17. Use of the compound according to claims 1-13 for the preparation of a medicament for the treatment of essential hypertension, congestive heart failure and renal failure.

Figure 1: XRPD pattern of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

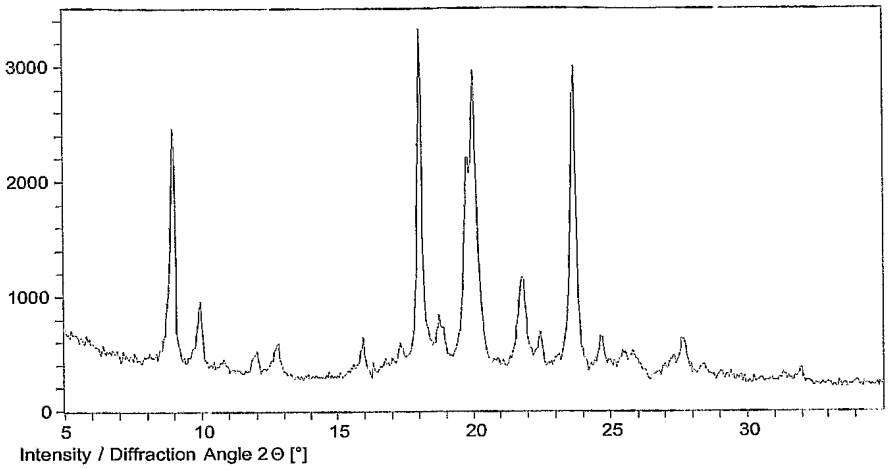


Figure 2: IR (ATR) spectrum of form polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

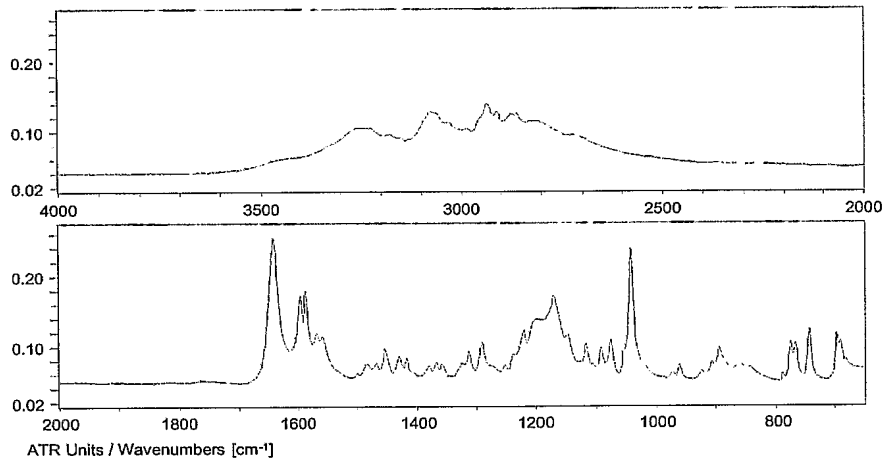


Figure 3: DSC trace of form polymorphic form α of *4*-(*4*-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

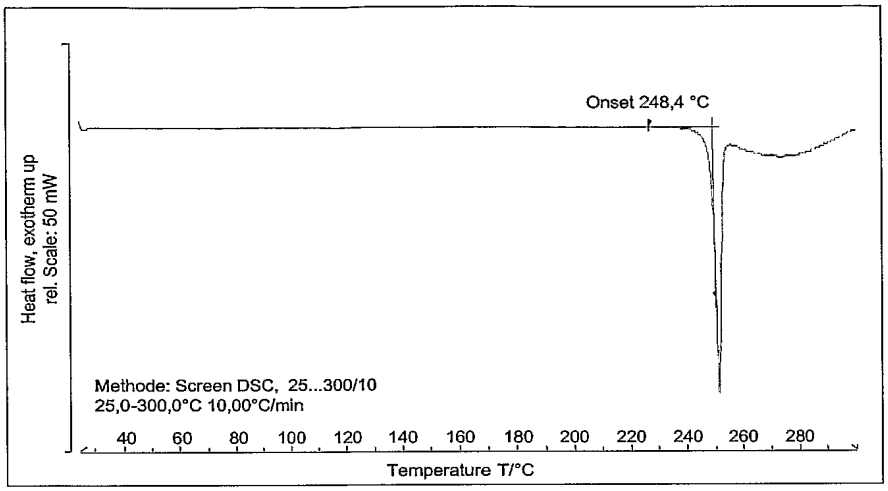


Figure 4 XRPD pattern of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

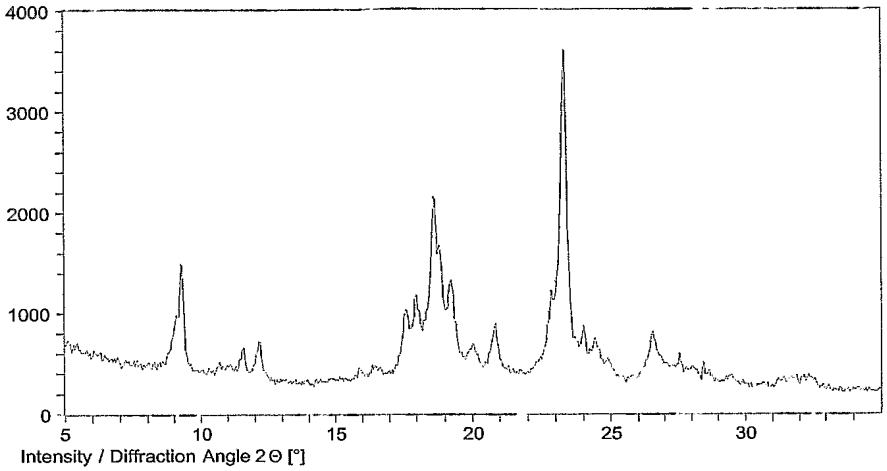


Figure 5 IR (ATR) spectrum of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

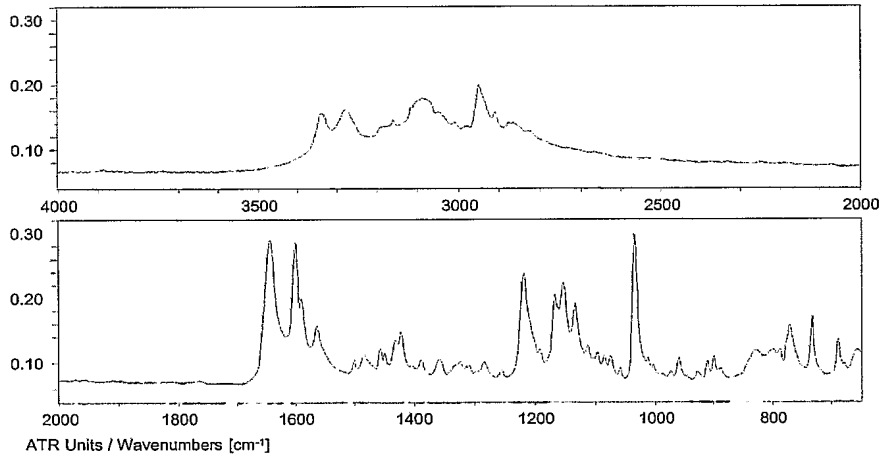
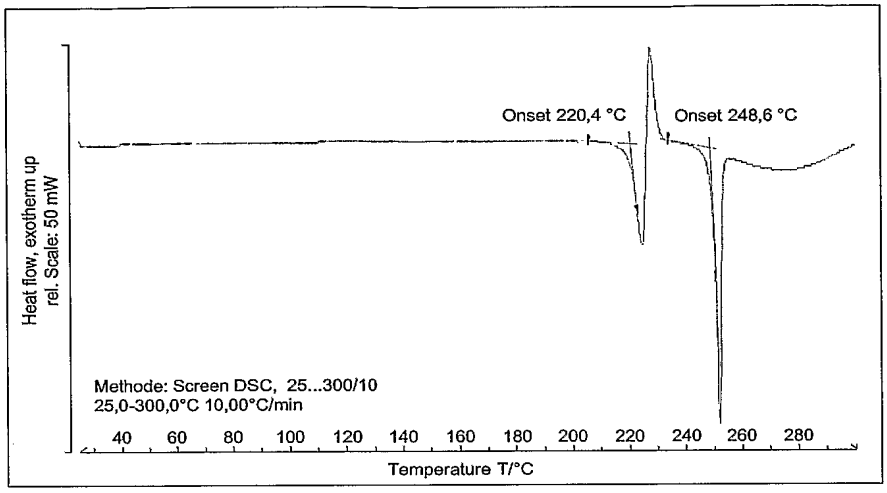


Figure 6: DSC trace of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate



INTERNATIONAL SEARCH REPORT

PCT/EP2004/050573

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/62518 A (CADUS PHARMACEUTICAL CORP ; MCKIBBEN BRYAN (US); WITTER DAVID J (US);) 9 December 1999 (1999-12-09) cited in the application page 70, lines 6-11; page 29, line 28 - page 30, line 9; claim 60	1-17
A	BERNSTEIN J ET AL: "Concomitant Polymorphs" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, VERLAG CHEMIE. WEINHEIM, DE, vol. 38, 1999, pages 3441-3461, XP002219563 ISSN: 0570-0833 introduction; section 3.2.6	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 July 2004	16/07/2004

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THRELFALL ET AL: "Analysis of Organic Polymorphs" ANALYST, LONDON, GB, vol. 120, October 1995 (1995-10), pages 2435-2460, XP002101807 the whole document	1-17

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